Remarks

Claims 1-48 currently are pending in the present case. The restriction requirement having been made final, Applicants are canceling claims 36-48, which are directed to a non-elected invention. Applicants reserve the right to prosecute the canceled subject matter in a later-filed divisional or continuation application. Claims 6-7 are withdrawn from consideration as directed to a non-elected species. Claims 1-5 and 8-35 have been examined. Applicants are adding new claims 49-52 with this amendment.

Claims 1-4, 17, 18, 23 and 27-29 are rejected as anticipated by Z'hu et al., who are cited for teaching a nucleic acid encoding a recombinant single-chain human MHC class II molecule comprising an antigenic peptide bond via a linker to the extracellular domain of the MHC class II beta chain. Z'hu et al. also are cited for teaching deletion of the beta chain transmembrane domain attachment of an MHC class II alpha chain extracellular domain with insertion of a truncation signal to delete the alpha chain transmembrane domain. The Office refers in particular to page 1934, second column, page 1935 and Figure 1, and asserts that this invention anticipates the claimed invention.

Applicants have amended claims 1 and 23 to incorporate the limitations of claims 5 and 26, respectively. The claims now recite that the peptide sequence (claim 1) and the pre-selected

peptide antigen (claim 23) are an autoantigen. The Z'hu et al. reference does not teach or suggest autoantigen peptides, as is implicitly conceded by the Office in failing to reject claims 5 and 26 under 35 U.S.C. § 102. Z'hu et al. also do not teach or even suggest autoimmune disease-associated Class II *MHC* molecules. The rejection therefore now is overcome because the cited reference does not teach all elements of the amended claims. Applicants request its withdrawal.

Claims 1-5, 8-12, 17-23, 26-29 and 35 are rejected as obvious over the combination of Z'hu et al. and Chao et al. The Office concedes that Z'hu does not teach glutamic acid decarboxylase peptides in association with MHC class II molecules, but cites Chao et al. for teaching GAD 65 peptides that bind to a murine MHC class II haplotype associated with diabetogenesis in NOD mice, including the instant SEQ ID NOS: 1 and 2. The Office Action relies on guidance in Z'hu et al. to provide the motivation to use the peptides of SEQ ID NOS: 1 and 2 with its engineered HLA molecules.

To make out a prima facie case of obviousness against a claim, the Office is required to make a showing as to all three of the following: (1) the cited references must teach or suggest all elements of the rejected claim; (2) the references or the prior art must provide motivation to combine or modify the teachings of the cited art to achieve the claimed invention; and (3) there must be a reasonable expectation of success for the

combined art. M.P.E.P. §2143. Failure to meet only one of these standards is fatal to a showing of prime facie obviousness.

The claims here rejected relate to a recombinant nucleic acid or protein which comprises (DNA encoding) an autoantigenic peptide that binds to a Class II *MHC* molecule and (DNA encoding) the extracellular protein of the β chain of that Class II *MHC* molecule. New dependent claims added herein recite autoimmune disease-associated Class II *MHC* molecules as well. Applicants refer the Office to paragraphs 5-7, 17 and 55, which discuss disease-associated Class II, for support for the new claims.

Z'hu et al. teach a recombinant Class II (HLA-DR1) molecule, three antigenic peptides (p25 from HIV GAG and two influenza peptides) which can bind to this molecule, and binding of bacterial superantigen. Thus, as the Office concedes, this reference does not anticipate any of the claims as amended and does not teach or suggest all the elements of claims 1 and 23, as amended. Chao et al. are cited to make up for the deficiencies of the Z'hu et al. reference. Chao et al. disclose four immunogenic epitopes of GAD 65 (see Table 2). Chao et al. do not teach that these peptides bind to a Class II molecule, nor do they suggest that recombinant nucleic acid molecules of the type required by the present claims should or could be made. Chao et al., to the contrary, imply that GAD 65 peptides presented by susceptible MHC Class II alleles might not even exist. See Chao et al., page 30, left column, lines 41-45 and page 33, right

column, lines 1-3. They do not suggest that the peptides they list in Table 2 are peptides that bind Class II or even that they should be tested for binding to Class II.

Chao et al. and Z'hu et al. in combination, even at best when ignoring the above statements by Chao et al., suggest only that GAD 65 epitopes would be "obvious to try," however, the authors of Chao et al. express a great deal of doubt as to potential success. Therefore, the references cited by the Office do not provide any meaningful motivation to achieve the invention claimed by Applicants, since there is no nexus between the ideas of recombinant Class II (HLA-DR1) molecules of Z'hu et al. and the GAD 65 peptides of unknown and doubtful binding to Class II (DRB1 *0405 or A^{g7}). The Office therefore has failed to meet the second necessary criterion for a prima facie case of obviousness.

Furthermore, there would have been no expectation of success whatsoever, even if the skilled person had attempted to combine the teachings of Z'hu et al. and Chao et al. First, the cited authors doubt even the existence of GAD peptides that bind to the Class II MHC. The cited art therefore not only fails to provide an expectation of success, but teaches away from the combination relied upon by the Office by implying that the claimed invention would not be successful.

The person of skill finds no motivation in the general art near the time of filing of this application. For example, Hackett and Sharma, *Nat. Immunol.* 3(10): 887-889, 2002, dated

October 2002, after the filing date of this application, discuss the difficulties still extant in producing Class II MHC-based reagents such as are claimed here. These authors summarize the consensus of a workshop earlier in 2002 at the NIAID: determining why some of these Class II reagents work and some do not is "an inexact science." See Hackett and Sharma, page 887, right column, lines 4-20. Some of the reasons for the greater unpredictability of binding to Class II are discussed in the following lines of the article, including contributions from both membrane-anchored chains, lowered stringency and conformational ambiguity of the peptides, differences in strength of binding, and more. Applicants also direct the attention of the Office to the accompanying declaration under 37 C.F.R. §1.132 by Dr. Liu, an inventor of this application. In this declaration, Dr. Liu provides further evidence that no reasonable expectation of success was found in the art at the time this application was filed.

Thus, applicants respectfully submit that production of autoantigen-binding MHC Class II molecules such as claimed here would not be expected to be successful by the skilled person because the science was known in the art to be unpredictable and unreliable. Z'hu et al. do not teach or suggest that autoimmune disease-associated peptides would work with their methods and

Chao et al. teach the opposite. Therefore, the Office cannot meet the third criteria necessary for making out a prima facie case of obviousness.

Applicants would like to point out that they believe they are the first to generate autoimmune disease-associated Class II MHC tetramer reagents and use them to isolate large members of autoreactive T cells. Persons in the art doubted that these recombinant molecules could be generated successfully prior to the success of Applicants here. See the accompanying Declaration under 37 C.F.R. §1.132 ("the Liu Decl."). Because the relevant art is highly unpredictable and there existed considerable doubt that the molecules claimed here could be produced, Applicants respectfully submit that the Office cannot make a showing of reasonable expectation of success for the pending claims.

For the above reasons, Applicants respectfully submit that the Office cannot make out a case of prima facie obviousness against the claims as amended. Applicants therefore request that this rejection be withdrawn.

Claims 1-5, 8-13, 15, 17-24, 26-30, 26-30 and 32-35 are rejected as obvious over Z'hu et al. in view of both Chao et al. and Crawford et al. The teachings of Crawford et al. with respect to multimerization of MHC class II/peptide complexes using biotin are combined with the disclosures of Z'hu et al. and Chao et al., which are asserted to teach MHC class II

transmembrane-truncated molecules and the GAD 65 peptides of SEQ ID NOS: 1 and 2.

The deficiencies in the combined disclosures of Z'hu et al. and Chao et al. are discussed at length above. Applicants refer the Office to these remarks and reassert that the combination of Z'hu et al. and Chao et al., do not render the instant claims obvious.

The Office cites Crawford et al. for teachings related to biotinylation of soluble MHC molecules and attachment of phycoerythrin/streptavidin complexes for stability. Crawford et al. do not teach or suggest the invention claimed here and do not make up for the deficiencies of the earlier-cited references. Crawford et al. do not provide any motivation to combine the Z'hu et al. and Chao et al. references or provide any reasonable expectation of success for such a combination if the skilled person were to happen upon it. Crawford et al. only suggest covalent attachment of peptides to the MHC molecule and multimerization using a biotinylated tag, but do not assist the Office in making out a prima facie case of obviousness against the claims here rejected. Applicants therefore request that this rejection be withdrawn because the Office cannot meet all of the necessary criteria for making out a prima facie case of obviousness based on this combination of references.

Claims 1-5, 8-12, 14, 16-23, 25-29, 31 and 35 are rejected as obvious over Z'hu et al. in view of Chao et al. and Rhode et al. Rhode et al. are cited for teaching oligohistidine tags.

The deficiencies of the Z'hu et al. and Chao et al. references are discussed above. In summary, these references provide no motivation to combine their disparate teachings because the references teach doubt even of the existence of the inventive compounds. Neither the cited references nor the art in general provide any reasonable expectation of success should the combination be attempted. Applicants refer the Office to the discussion above and the accompanying Liu Declaration, which provide evidence that the art provided no expectation of success for the present invention.

The Rhode et al. reference does not make up for the deficiencies of Z'hu et al. and Chao et al. This reference is cited for its teachings related to oligohistidine tags. Nothing in this reference provides a motivation to combine the teachings of Z'hu et al. and Chao et al. to achieve the invention claimed here or provides any reasonable expectation that such an unlikely combination would be successful merely because of the additional presence of a histidine tag. Applicants respectfully submit that the Office cannot make out a prima facie case of obviousness against the claims pending here and request that this rejection be withdrawn.

Applicants submit that the rejections currently pending are not proper with respect to the amended claims and therefore request favorable consideration of the amended claims at this time.

Respectfully submitted,

By _____

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